

Dennis M. Erb, Ph.D.  
Senior Director  
Regulatory Affairs

Merck & Co., Inc.  
P.O. Box 4, BLA-20  
West Point PA 19486  
Tel 610 397 7597  
215 652 5000  
Fax 610 397 2516

August 27, 1999

1683 98 07 10 19:25

Dockets Management Branch (HFA-305)  
Food and Drug Administration  
5630 Fishers Lane Rm. 1061  
Rockville, Maryland 20852



Docket No. 99D-0529  
Draft Guidance for Industry on Changes  
to an Approved NDA or ANDA

Merck & Co., Inc. is a leading worldwide, human health product company. Merck's corporate strategy -- to discover new medicines through breakthrough research -- encourages us to spend more than \$2 Billion, annually, on worldwide Research and Development (R & D). Through a combination of the best science and state-of-the-art medicine, Merck's R & D pipeline has produced many of the important pharmaceutical products on the market, today.

Merck supports regulatory oversight of product development that is based on sound scientific principles and good medical judgment. Regulators must be reasonable, unbiased and efficient when they review the quality, effectiveness and safety of our products. It is in both of our interests to see that important therapeutic advances reach patients without unnecessary or unusual delays.

As an innovative research and development company, Merck constantly explores new indications, uses, and improved manufacturing efficiencies of our approved drug products. The results of this effort often necessitates supplementing the approved NDA. Thus Merck is affected by regulations which impact the reporting requirements and implementation of changes to an approved NDA. For these reasons, we are very interested in and well qualified to comment on this Draft FDA guidance to provide recommendations to holders of NDA's and ANDA's who intend to make post-approval changes in accordance with Section 116 of the Food and Drug Administration Modernization Act (FDAMA).

#### **GENERAL COMMENTS:**

The draft guidance as written does not meet the full intent of FDAMA, in that it increases rather than reduces the regulatory burden for post-approved changes. Several new reporting requirements beyond the current regulation (21CFR314.70), appear in the draft guidance. Further, the guidance does not fully embrace the concept of categorization of changes based on the potential to have an adverse effect on the quality and safety of the product. It appears that this guidance merely incorporates the existing submission requirements of 21CFR314.70 plus additional GMP related items into the newly designated categories of major, moderate, and minor changes.

99D-0529

C 22

Given the current level of checks and balances provided by specifications and validation testing, several changes presented in the guidance as major changes requiring prior approval supplements should be given consideration to a reduced reporting requirement. We encourage an open dialog between FDA and industry in assessing the potential impact of changes noted in this guidance and the proposed revisions to 21 CFR 314.70.

As previously mentioned, the draft guidance introduces new reporting requirements particularly for GMP related items. We believe that GMPs should not be incorporated into 21CFR314.70. GMP regulations are sufficiently documented in 21CFR210 and 211. Inclusion of GMP activities as reportable items will substantially increase the number of supplements and regulatory burden on industry without increase assurance of quality over current practices. We strongly recommend the removal of GMP related items from this guidance.

### Specific Comments

## **Section II. Reporting Categories**

Line 46: In defining a Major Change as one that requires a prior approval supplement, FDA includes changes that may affect the safety of the product. This may be somewhat confusing as it is conflicting with the regulation 21CFR314.70(c) which requires safety changes (now defined as moderate changes) to be submitted as changes being effected. The guidance should be clear not to group label changes to strengthening safety statements as prior approval supplements.

Line 68: The use of the word “may” makes it unclear when the FDA will identify certain moderate changes for which distribution of the product can occur upon receipt of the CBE. This guidance identifies certain moderate changes which can be implemented upon receipt of a CBE but is not all inclusive. A mechanism to update the list of changes should be identified in this guidance.

Lines 79-84: The Guidance and the proposed rule should define in which instances a comparability protocol may be used. Further, it should be clearly stated that comparability protocols can be submitted in the original application.

## **Section III. General Requirements**

Lines 86-87: FDA requires notification of changes beyond the variations allowed in the application. In some instances throughout the Guidance, “a change to the approved application” or “changes that are materially different from the approved application” are used and in others it simply refers to “a change”. We believe that the terminology “changes that are materially different from the approved application” is the most appropriate description and should be used consistently throughout the document.

Lines 88-89: The listing of all changes included in a supplement or annual report in the cover letter is redundant and potentially unwieldy. A summary of the type of changes should be sufficient in the cover letter since the changes are outlined in detail in the supplement and Annual Report

Line 97: This guidance should acknowledge the existing guidance which allows for the electronic submission of labels<sup>5</sup> as opposed to 12 copies of final print labeling.

#### **Section IV. Assessing the Effect of Manufacturing Changes**

Line 105: For clarity, we strongly recommend using the term “assess” instead of “validate”, throughout the document.

Line 108: Please differentiate between the terms “strength” and “potency”.

Line 145: Reference to the ICH Impurity Guideline would be useful to clarify that impurities greater than ICH levels will be qualified or identified, as appropriate.

Lines 171-174: We disagree with the global statement that all changes which adversely affect the product must be filed as a prior approval supplement. In some cases improvement in one quality parameter may be offset with an acceptable decline in another. Provided the product meets the approved specifications, the reporting requirement should follow the category established for a specific type of change.

Lines 176-179: If identification of a new low level impurity shows that there are no issues, such as identification of a known metabolite or previously qualified compound, the change would not adversely impact the product. Why does the Agency consider this an “adverse effect”, requiring prior approval? This information should be filed as a CBE supplement.

#### **Section VI. Sites**

General comments: This section, while providing a high level of detail, is written in a confusing manner. A chart or a table, such as those provided in the Draft Stability Guidance would be very helpful. Additionally, separating manufacturing from packaging site changes may provide for simplified descriptions. Further, we propose that clear definition should be provided for site and facility terms and that these terms be used consistently throughout this section.

Footnote to line 198: Clarify which procedures would constitute container closure preparation, in addition to sterilization.

Lines 211-221: These lines are redundant with lines 248-261 and should be removed to reduce confusion.

Line 212: Clarification as to the meaning of “type of operation” is needed.

Lines 239-243: These generalized statements do not provide sufficient detail to be useful and can lead to confusion. The detail is included in the subsequent sections.

Lines 248-249 and 253-255: It is unclear if these sections include primary packaging and in-process manufacturing sites. Based on lines 314-315, secondary packaging sites should be excluded from these sections. Clarification is needed.

Lines 256-261: It is unclear if this section includes primary packaging and in-process manufacturing sites. Based on lines 303-309, drug substance intermediates should be excluded from this section. Based on lines 314-315, secondary packaging sites should be excluded from this section.

Lines 259-260: Contamination precautions are primarily GMP concerns, not product-specific issues and therefore, should not be included in the approved application.

Lines 271-276: If a sterile product site transfer into a facility with a barrier system is submitted as a prior approval supplement, can the subsequent transfer of similar products into the facility each be submitted in a CBE +30 days?

Lines 277-279: These statements lead to confusion and may be simplified by incorporation of these statements into lines 262-276.

Lines 294-300: The movement of a testing facility to a different campus given the criteria provided in this section represents a minimal potential to adversely affect the product. Therefore, we propose that an annual report as opposed to a CBE-30 be the method of supplementing the application.

Lines 303-309: Changes within the same campus for drug substance intermediates should have minimal potential to adversely affect the product, since the entire campus operates under the same procedures, compliant with cGMP's. We consider Agency notification of this change to be excessive. If the new area has undergone a satisfactory cGMP inspection within 2 years, for a similar type of operation, no notification is necessary.

Line 306: Based on lines 328-332, final drug substance intermediates should be excluded.

Lines 314-316: Changes to the secondary packaging or labeling site, when the secondary package is providing no protection to the product, should have no adverse effect on the product. We consider Agency notification of this change to be excessive.

Line 317: Changes within the same campus for testing facilities should have no adverse effect on the product, since the entire campus operates under the same procedures and the methods are validated. We consider Agency notification of this change to be excessive.

Lines 319-322: Changes within the same campus for non-sterile drug substance, in-process material, or drug product should have no adverse effect on the product and we consider Agency notification of this change to be excessive.

Lines 319-322 conflict with 303-304. Lines 319-322 require that a move to a site on the same campus for a non-sterile drug substance can be filed as an annual report item, but the same move for the final intermediate needs to be filed as a CBE, as indicated by lines 303-304.

Lines 333-336: Information regarding site floor plans and manufacturing areas should not be included in a NDA, but be maintained at the facility in the event of an inspection. We do not feel that it is appropriate to include this information in the Guidance.

## **Section VII. Manufacturing Process**

Lines 354-360: These lines are redundant with the Section B. that follows and should be removed to reduce confusion.

Lines 370-401: Many of the items in this section also appear in the November 1994 Guidance for Industry for Sterilization Process Validation Documentation. As stated in our general comments, we believe that these items are adequately addressed by cGMP's and need not be filed in the NDA.

Line 373: Please provide examples of changes in the sterilization method(s) that require a prior approval (e.g. changes to D value). We suggest that only changes requiring re-validation be submitted.

Line 380: Deletion of non-critical equipment would be more appropriately filed as a CBE, based on the Guidance's General Considerations.

Lines 413-414: These items should be listed in the section on drug substance (lines 415-420).

Line 414: We recommend deleting line 414 since changes to route of synthesis is covered in lines 416-410.

Line 416: "Any" changes should be clarified. We suggest the use of changes which results in a significant adverse effect.

Line 423: This guidance often refers to the use of a particular component in other CDER-approved products. How will the Agency notify industry of the CDER-approved components?

Lines 466-467: If the manufacturing of an early intermediate is transferred to a contract manufacturer not previously listed in the application, then this would be filed as a CBE, as per lines 305-309. Please clarify that a CBE + 30 days, would be required if, at the same time, we redefine the intermediate as a starting material.

Line 482: Please clarify if “except as otherwise noted” refers to this document or to SUPAC as well. In SUPAC, the filing strategy for a change in batch size is dependent on the extent of the change, but in this Draft Guidance it is not. This document should be aligned with other appropriate final guidances.

Lines 483-487: “Except as otherwise listed”, should be added for clarity to exclude modified release products.

Line 491: Changes to the order of mixing should be expanded to include solutions used in the manufacture of solid oral dosage forms, such as granulating solutions or film-coating solutions or suspensions.

Lines 494-499: Indicate that all changes to specifications (including container closure systems) listed within the approved application must be submitted in a prior approval supplement. Copies of drawings for primary packaging materials and components are normally filed with NDA’s. However, minor changes to components such as a change to the shoulder of a bottle would not adversely impact the product and thus a reduced reporting requirement should be permitted.

## **Section VIII. Specifications**

Lines 508-512. It is not clear whether the USP supersedes approved analytical procedures. If “regulatory analytical procedure” was replaced with “USP method” in line 512 it would be clearer.

Lines 538, 551 and 578: “Any” changes should be clarified. We suggest “any changes that require validation” or “any significant” changes.

Lines 567-571: The requirement that *changes to comply with an official compendium must be consistent with FDA requirements and provides the same or greater level of quality assurance* is a deviation from the current acceptable practice and represents an increase in criteria over the current 21CFR314.70. We recommend that all changes to comply with an official compendium remain as annual reportable items and that the additional criteria presented in this section deleted.

Lines 584-585: Tightening of specifications for existing reference standards are currently non-reportable changes. Typically a certificate of analysis is submitted in the application for the reference standards rather than a unique set of specifications. We recommend deletion of this item from the guidance.

## **Section IX. Package**

Lines 607-624: Packaging change requirements... Many of the requirements in this section represent new more restrictive filing requirement that are in opposition to the spirit of FDAMA. A scientific based approach to classifying packaging changes is needed.

Lines 597-606: These lines are redundant with Section B. that follows and should be removed to reduce confusion.

Line 647: It should be clarified if the addition of a new container closure system, where the package does not control delivery of the drug, is covered in this statement.

Line 653: The following items are not listed and should be included as annual report changes: Change in tablet count; change in packaging component supplier; change in bottle or closure color, changes in registered blister card design (cavity sizes, sealing border dimensions, blister lay-out) and change to dessicants.

Line 672: Does “changes” include the addition or deletion of items that control odor?

## **Section X. Labeling**

Line 736: Consideration should be given to reduced reporting requirements for tightening of storage condition due to post market stability studies.

Line 745: The existing guidance which allows for the electronic submission of labels should be noted.

## **Section XI. Miscellaneous Changes**

Lines 779-781 and lines 790-792: These sections should differentiate between extension of expiry based upon extrapolation of data and extension based on shelf-life data.

Lines 779-781 and lines 790-792: While this section is consistent with the Draft Stability Guidance, June 1998, and the proposed changes to 314.70, we disagree that pilot scale batch stability data, generated as per an approved protocol, can not be used for extension of expiry. Pilot scale batches can be used to establish expiration dating in the original NDA. The extension of an expiration date based on data from these batches should also be acceptable. We recommend that the guidance allow for extension of expiration dating based on pilot batches using an approved stability protocol.

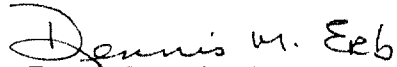
## Glossary

General Comment: There should be a definition for "CDER approved [*component, ink, etc*]".

Line 821: As per lines 122-123, component can include packaging, drug substance, etc.

We trust that these comments will be considered in further development of the draft guidance. We encourage an open dialog between FDA and industry in revising this guidance and development of the companion re-write of 21 CFR314.70

Sincerely,

Handwritten signature of Dennis M. Erb in black ink.

Dennis M. Erb, PhD.

Sr. Director, Regulatory Affairs

Q:ligi/guidance/305

Federal Express 810419612929

# FedEx USA Airbill

FedEx  
Tracking  
Number

810419612929

Form  
10 No

0210

Recipient's Copy

1 From 8/27/99

Sender's name Dr. Dennis Erb Phone (610) 397-7597

Company MERCK RESEARCH LABORATORIES

Address 5 GENTRY PKWY BLDG 20

City BLUE BELLS State PA ZIP 19422

2 Your Internal Billing Reference Information

3 To Documents Management Branch HFA305  
Phone

Company Food & Drug Administration (HFA-305)

Address 3600 Fishers Lane, Room 1051  
Dept./Floor/Suite/Room

City Rockville, State MD ZIP 20852

**For HOLD at FedEx Location check here**

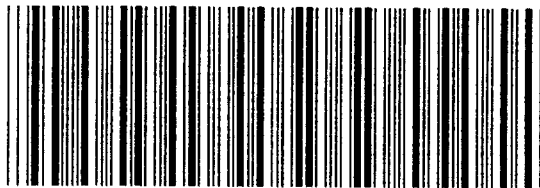
☐ Hold Weekday  
(Not available with  
FedEx First Overnight)

☐ Hold Saturday  
(Available for FedEx Priority Overnight  
and FedEx 2Day only)

**For WEEKEND Delivery check here**

☐ Saturday Delivery  
(Available for FedEx Priority  
Overnight and FedEx 2Day only)

☐ NEW Sunday Delivery  
(Available for FedEx  
Priority Overnight only)



8 1 0 4 1 9 6 1 2 9 2 9

**4a Express Package Service Packages under 150 lbs.**

☒ FedEx Priority Overnight (Next business morning)  
☐ FedEx Standard Overnight (Next business afternoon)  
☐ FedEx First Overnight (Earliest next business morning delivery to select locations) (Higher rates apply)  
☐ FedEx 2Day (Second business day)  
☐ FedEx Express Saver (Third business day)

**4b Express Freight Service Packages over 150 lbs.**

☐ FedEx Overnight Freight (Next business day)  
☐ FedEx 2Day Freight (Second business day)  
☐ FedEx Express Saver Freight (Up to 3 business days)

(Call for delivery schedule. See back for detailed descriptions of freight services.)

**5 Packaging**

☒ FedEx Letter ☐ FedEx Pak ☐ FedEx Box ☐ FedEx Tube ☐ Other Pkg

**6 Special Handling**

Does this shipment contain dangerous goods? ☐ No ☐ Yes (One box must be checked)  
☐ Dry Ice (Dry Ice, 9, UN 1845) ☐ Yes Shippers Declaration ☐ Yes Shipper's Declaration  
☐ Cargo Aircraft Only

**7 Payment**

Bill to: ☒ Sender ☐ Recipient ☐ Third Party ☐ Obtain Recipient  
Account No. in Section 1 will be billed. (Enter FedEx Account No. or Credit Card No. below) ☐ Credit Card ☐ Cash/Check

Total Packages Total Weight Total Declared Value\* Total Charges

\*When declaring a value higher than \$100 per item, you pay an additional charge. See SERVICE CONDITIONS, DECLARED VALUE, AND LIMIT OF LIABILITY section for further information.

**8 Release Signature**

Your signature authorizes Federal Express to deliver this shipment without obtaining a signature and agrees to indemnify and hold harmless Federal Express from any resulting claims.

**Questions?**

Call 1-800-Go-FedEx (800) 463-3339

321

0083284960

FORM 1000-1000  
Rev. 08/98  
Form #15302200  
© 1998 FedEx  
Printed in U.S.A.